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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,886	08/31/2006	Mahin D. Maines	176/61623	4129

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,886	MAINES, MAHIN D.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *2,11,13 and 17-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-10,12 and 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/27/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group 4, claims 1, 3-10, 12 and 14-18 and the species of protein kinase C (PKC) in the reply filed on December 22, 2008 is acknowledged.

Claims 2, 11, 13 and 17-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 22, 2008.

Claims 1, 3-10, 12 and 14-16 are examined on the merits.

Claim Objections

Claims 10 and 16 are objected to because of the following informalities: In the amendments submitted December 22, 2008 applicants have added PKC, protein kinase C, to the Markush group of claims 10 and 16. Applicants point to table 1 in example 4 as providing support for this amendment. Table 1 provides support only for the alpha isoform, therefore the election of species is considered to be PKC alpha and the claims should be amended to reflect this. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-10, 12 and 14-16 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2 and 5 of U.S. Patent No. 6,969,610. Although the conflicting claims are not identical, they are not

patentably distinct from each other because the patented claims are directed to a species of the instant invention. The '610 claims are directed to a method of modifying cell structure by administering a vector that encodes a biliverdin reductase that hybridizes to SEQ ID NO: 2. This biliverdin reductase that hybridizes to SEQ ID NO: 2 is a species of the instant claims, which are directed to methods comprising the step of increasing biliverdin reductase by administering a construct that encodes any biliverdin reductase, not only those that hybridize to SEQ ID NO: 2. Although the instant claims recite a intended effect of administration that is different from the claimed effect of the '610 method, because the step is the same the methods are considered to be obvious variants and performing the '610 method is assumed in the absence of evidence to the contrary to provide the effect recited in the instant claims.

Claims 1, 3-10, 12 and 14-16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-11, 13-21 and 39 of copending Application No. 10/499,243. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '243 claims are directed to a method that comprises the identical step of the instant claims: increasing biliverdin reductase by administering a construct that encodes biliverdin reductase. Although the instant claims recite a intended effect of administration that is different from the claimed effect of the '243 method, because the step is the same the methods are considered to be obvious variants and performing the '243 method is assumed in the absence of evidence to the contrary to provide the effect recited in the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 3-10, 12 and 14-16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1, 4-8, 11-16 and 18-22 of copending Application No. 11/816,557. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '557 claims are directed to a method that comprises the identical step of the instant claims: increasing biliverdin reductase by administering a construct that encodes biliverdin reductase. Although the instant claims recite a intended effect of administration that is different from the claimed effect of the '557 method, because the step is the same the methods are considered to be obvious variants and performing the '557 method is assumed in the absence of evidence to the contrary to provide the effect recited in the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-10, 12 and 14-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are directed to methods of modifying expression of cell cycle and cell signaling proteins by modifying the concentration of biliverdin reductase or fragments or variants thereof. In specific embodiments the concentration of biliverdin reductase is increased by administration of biliverdin reductase or fragments or variants.

Paragraphs cited when describing the teachings of the specification refer to the pre-grant publication of the instant application. The specification teaches at paragraphs 32 and 33 that numerous domains of biliverdin reductase have been identified and contemplates that the homologous sequences from other mammalian species can be used. These homologues are contemplated as containing differing degrees of sequence identity. At paragraph 36 the instant specification describes that preferred fragments used in the invention include the leucine zipper and nuclear localization signals. Variants of biliverdin reductase are described at paragraphs 41-44 as including additions, deletions and substitutions, but the specification does not describe to what degree biliverdin reductase can be modified and still be considered biliverdin reductase. The prior art does not teach that biliverdin reductase increases the expression of cell cycle or cell signaling proteins, therefore only the instant specification can be relied upon for written description support of the claimed method. With regard to the elected cell signaling protein of protein kinase C alpha, the specification describes in example 4

that microarray analysis of total RNA from cells transformed with a vector expressing biliverdin reductase demonstrate a 2.4 fold increase in PKC-α expression.

The claims embrace the treatment of diseases associated with PKC-α by increasing PKC-α expression. The specification describes several proteins embraced by the claims and the conditions associated with these proteins, but no description of PKC-α is found in the specification except the teaching in table 1 that this gene is expressed in response to biliverdin reductase expression. Therefore, the genus of diseases that can be treated by increasing PKC-α expression is not described.

The claims embrace the use of numerous sequences that constitute biliverdin reductase and its homologs, fragments and variants in order to increase the concentration of other proteins that are cell cycle or cell signaling proteins. The genus of sequences embraced by the instant claims is large, and while numerous domains of biliverdin reductase have been identified, the specification provides no description of which domains of biliverdin reductase provide the function of increasing expression of other proteins such as PKC-α. Without description of a correlation between the various domains that make up biliverdin reductase and the function of increasing the concentration of cell cycle and cell signaling proteins, the skilled artisan would not know what sequences embraced by the genus of fragments or variants would be functional in the claimed method. For example, while the instant specification teaches that a preferred fragment of biliverdin reductase is one containing the leucine zipper motif, the specification has not demonstrated that this is a motif essential to the claimed function of increasing expression PKC-α, therefore a correlation between the structure of

biliverdin reductase and the claimed function of increasing expression of PKC-α is lacking.

In order for the written description provision of 35 USC 112, first paragraph to be satisfied, applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed. For example, MPEP 2163 states in part,

> "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."

The skilled artisan cannot envision the detailed structure of the encompassed fragments and variants of biliverdin reductase that induce expression of other cell cycle or cell signaling proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

Therefore, the full breadth of biliverdin reductase fragments and variants encompassed by the claims do not meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant.

Claims 12 and 14-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

The claims are directed to a method of treating a condition associated with an expression level of a cell signaling protein that is PKC-α by increasing the concentration of biliverdin reductase.

The prior art recognizes that there are some conditions where PKC-α is overexpressed that may benefit from inhibition of this protein. See WO 95/25712, which teaches that PKC activation is implicated in diseases such as cancer, cardiovascular and renal disorders, inflammation, immunosuppression, septic shock and central nervous system disorders. The prior art is silent with regard to what conditions are associated with underexpression of PKC-α such that the claimed method of increasing this protein through increasing biliverdin reductase will provide a treatment effect.

Because the prior art is silent with regard to conditions that will benefit from increased expression of PKC-α, enablement of the claimed methods must be found in the specification as filed. The specification teaches that increase of biliverdin reductase provides an increase of expression of the alpha isoform of protein kinase C (PKC-α). The specification provides no further discussion of this protein and provides no information about conditions associated with this protein that can be treated using the claimed methods.

Therefore, in order to practice the claimed method of treating conditions associated with PKC-α, the skilled artisan would have to engage in undue, trial and error experimentation to determine which conditions would benefit from increased expression of PKC-α.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3-6, 9, 10, 12 and 14-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Bach et al. (US 2004/0131703).

The claims are directed to a method of modifying expression of a cell signaling protein such as PKC-α or treating a condition associated with an expression level of a

cell signaling protein such is PKC-α by increasing the concentration of biliverdin reductase. In specific embodiments, the biliverdin reductase concentration is increased by administering biliverdin reductase or a construct expressing the gene. The delivery can be via liposomes.

Bach et al. disclose at paragraph 77 a method of expressing or administering biliverdin reductase to a patient in order to increase bilirubin levels. The biliverdin reductase can be delivered to a patient in liposomes or can be generated in a patient by gene transfer using an expression vector. Although Bach et al. do not disclose that administration of biliverdin reductase will have the effect of modifying expression of a cell signaling protein such as PKC-α or treating a condition associated with expression level of a cell signaling protein such as PKC-α, because the method disclosed by Bach et al. discloses the same step as the instant claims, the method of Bach et al. is assumed in the absence of evidence to the contrary to provide the claimed effects.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-10, 12 and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bach et al. as applied to claims 1, 3-6, 9, 10, 12 and 14-16 above.

Claims 1, 3-6, 9, 10, 12, 14-16 are described in the previous rejection. Claim 7 recites that the delivery vehicle is a fusion protein and claim 8 recites that the claimed method is performed on a cell *ex vivo*.

The teachings of Bach et al. are described in the previous rejection. This reference does not explicitly teach that biliverdin reductase be administered to a cell ex vivo or administered as a fusion protein, but the disclosure of the method of administering biliverdin reductase is part of a broader disclosure of several other types of proteins associated with heme degradation. Bach et al. do contemplate the use of fusion proteins to deliver both HO-1 and ferritin (see paragraphs 66 and 82) and further suggest that the pharmaceutical compositions of their invention can be delivered through an *ex vivo* method of gene therapy (see paragraphs 147 and 152). Therefore, it would have been obvious to one of ordinary skill in the art that the delivery methods contemplated for some of the active ingredients taught by Bach et al. could be used for delivery of biliverdin reductase and that these delivery methods could be easily adapted for delivery of this particular protein using routine methods.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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